UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

13

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/883,848	06/18/2001	Leona E. Ling	CIBT-P01-119	9957

28120 7590 12/28/2006

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
ONE INTERNATIONAL PLACE
BOSTON, MA 02110-2624

EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/28/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/883,848	LING ET AL.	
	Examiner	Art Unit	
	Brandon J. Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,26 and 37-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 26 and 37-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Response to the Amendment

The Amendment filed on 10/02/2006 in response to the previous Non-Final Office Action (03/30/2006) is acknowledged and has been entered.

Claims 1-2, 26 and 37-57 are currently pending under consideration.

The Declaration under 37 CFR 1.131 filed on 03/23/2005 is insufficient to overcome the rejection of Claims 1-2, 26 and 37-42 under 35 U.S.C. 103(a) based upon Porter et al. (US 6,613,798, 2003) as set forth in the last Office action because: The declaration by Leona Ling sets forth the conception and articulation of specific experiments designed to confirm the effects of hedgehog signaling on angiogenesis, wherein it was realized that exemplary agents including hedgehog protein, lipophilic modified hedgehog proteins, as well as other agonist of hedgehog signaling could be used to activate hedgehog signaling, thereby promoting angiogenesis. Specifically, the declaration (Exhibit 2) depicts the results of an exemplary experiment showing the reduction to practice of promoting angiogenesis using a hedgehog agonist, wherein the hedgehog agonist appears to be sonic hedgehog protein. Thus, while the declaration sets forth the conception of a genus of agonist and the reduction to practice a specific species, i.e. a polypeptide, the declaration is silent on the specific chemical structure of the other hedgehog agonists, specifically the small organic molecules as described in claim 1. Thus, the Declaration does not appear to be commensurate in scope with the instant claims.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Rejections Maintained:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the

subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 26, 37-38 and 42 **remain** rejected and new claims 43-57 **are** under 35 U.S.C. 103(a) as being unpatentable over Porter et al. (US 6,613,798, 2003) as evidenced by Pettet et al. (Proc. R. Soc. Lond. B 1996; 263: 1487-1493) in view of Ferrari et al. (Basic Res. Cardiol. 1995; 90: 52-54).

Porter et al teach small organic agonist that are capable of promoting proliferation in cells by modulating the hedgehog pathway, wherein the small organic agonists encompasses the claimed small organic compounds of formula XII (column 6, formula I and column 19, lines 3-10). With regards to the hedgehog pathway, the patent teaches that the small organic agonist can modulate the signal transduction pathway regulated by hedgehog, pathched (ptc), gli and/or smoothened (column 18, lines 40-43). Moreover, Porter et al. teach (column 54, lines 19-25) that the small organic agonist may be administered to a patient suffering from severe congestive heart failure (CHF) characterized by cardiac cachexia, as well as for promoting wound healing resulting from surgery, wherein the wound heals with less scarring (column 61, lines 8-27). With regards to the administration, the patent teaches that the agonist may be administered systemically (column 67, lines 1-8). Thus, while Porter et al. does not teach that wound healing is the promotion of angiogenesis, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure because as evidenced by Pettet et al., angiogenesis, the formation of blood vessels, is described as a process whereby capillary sprouts are formed in response to externally supplied chemical stimuli and occurs during wound healing (abstract). See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Porter et al. do not explicitly teach a method of improving myocardial function following myocardial ischemia, wherein the agonist promotes angiogenesis.

Ferrari comments on the clinical relevance of chronic left ventricular dysfunction, also referred to as "hibernating myocardium" (abstract). Specifically, the reference teaches that this condition may be present over months or years, or indefinitely in subjects with fibrosis, scar formation and remodeling after myocardial infarction, wherein the therapeutic implication with regards to regional and global left ventricular function due to hibernation will improve after

revascularization and it is associated with improved survival (page 52, 1st column, 2nd to 3rd paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer to a patient a small organic hedgehog agonist as taught by Porter et al. following myocardial ischemia in view of Ferrari. One would have been motivated to do so because Ferrari teaches hibernating myocardium is identified by scar formation following myocardial infarction and can be improved after revascularization, e.g., angiogenesis. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to a patient a small organic hedgehog agonist as taught by Porter et al. following myocardial ischemia in view of Ferrari, one would achieve a method of improving the survival of a patient following myocardial infarction.

In response to this rejection, Applicants note that US Patent 6,613,798 has a filing date which is later than the priority date of the present application and continue to contend that the declaration of Leona Ling under Leona Ling under 37 CFR 1.131 establishes "reduction to practice prior to the effective date of the reference, or conception of the invention prior to the effective date of the reference coupled with due diligence from said date to a subsequent reduction to practice or to the filing of the application. Therefore, Applicants contend that US Patent 6,613,798 is not available as prior art against the present application, and that this rejection cannot stand absent Porter et al. In addition to Applicants' contention that Porter et al. is not available as prior art, Applicants assert that the combination of Porter et al., Pettet et al., and Ferrari et al. fail to satisfy a prima face of obviousness. For example, Applicants contend the following: (1) Ferrari et al. comment on hibernating myocardium and its revascularization, but makes no mention or suggestion of hedgehog agonists or the treatment of ischemic conditions; (2) Pettet et al. teach that angiogenesis is involved in would healing, but fails to teach or suggest that hedgehog agonists could be useful as angiogenic agents, or that myocardial function following ischemia may be improved by promoting angiogenesis; and (3) Porter et al. teach small molecule hedgehog agonists which can promote neuromuscular growth, not vascular growth, which may be used in the prevention and/or reduction of the severity of neurological conditions deriving from, among other causes, vascular injury and deficits such as ischemia resulting from stroke (column 46, lines 1-7 of Porter et al.), but does not teach that the agonists can be used to promote vascularization or angiogenesis. Accordingly, Applicants contend that there is no common link between these cited disclosures that

would have motivated a person skilled in the art to combine these teachings with a reasonable expectation of success of arriving at the claimed invention. Thus, Applicants assert that it is the teachings of the present application that provide the motivation to use hedgehog agonists in the claimed method and the reasonable expectation of successfully using hedgehog agonist in the claimed method. However, Applicants assert that the Federal Circuit has been clear that both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicants' disclosure, see In re Vaeck, 947 F.2d 488, 493 (Fed. Cir. 1991). Additionally, Applicants contend that the criteria for assessing obviousness clearly acticulated by the Federal Circuit precludes the cobbling together of individual references, each of which teaches elements of the claimed invention, in an attempt to amass a facsimile of the claimed invention. For example, Applicants point to Gore & Associates, Inc vs. Garlock 721 F. 2d 1540, 1552 (Fed. Cir. 1983), wherein the Federal Circuit stated that "the district court lost sight of the principle that there must have been something present in those teachings to suggest to one skilled in the art that the claimed invention before the court would have been obvious." Moreover, Applicants assert that the Federal Circuit has reiterated these standards in more recent cases. See In re Kotzab, 217 F.3d 1365 (Fed. Cir. 2000); Princeton Biochemicals, Inc. v. Beckman Coulter, Inc., 411 F.3d 1332 (Fed. Cir. 2005). Thus, Applicants assert that the case law clearly establishes that to render the claimed invention obvious, there must be a motivation to specifically combine Porter et al., Pettet et al., and Ferrai et al. to arrive at the claimed invention, and this motivation must be grounded in the prior art references themselves, not in Applicants' disclosure.

These arguments have been carefully considered, but are not found persuasive.

In response to Applicants assertion that, in view of the current priority date and Declaration by Leona Ling under 37 CFR 1.131, US Patent 6,613,798 (referred also as Porter et al.) does not constitute prior art, the Examiner recognizes that, as set forth in the prior Non-Final Office Action of 7/15/2004, a priority date of June 18, 2001 was established for the small organic agonists encompassed by formula (XII) claimed in claim 1. As such, it is the Examiners opinion that US Patent 6,613,798 was filed prior to the instant application. With regards to the declaration, as stated above, the Declaration under 37 CFR 1.131 filed on 03/23/2005 is insufficient to overcome the rejection because the Declaration does not appear to be commensurate in scope with the instant claims. For example, the declaration (Exhibit 2) depicts the results of an exemplary experiment

showing the reduction to practice of promoting angiogenesis using a hedgehog agonist, wherein the hedgehog agonist appears to be sonic hedgehog protein. Thus, while the declaration sets forth the conception of a genus of agonist and the reduction to practice a specific species, i.e. a polypeptide, the declaration is silent on the specific chemical structure of the other hedgehog agonists, specifically the small organic molecules as described in claim 1. In response to applicant's arguments against the references individually, the Examiner recognizes that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). It must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which make up the state of the art with regard to the claimed invention. Furthermore, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, the Examiner recognizes the following: (1) Porter et al teach small organic agonist which encompass the claimed small organic compounds of formula XII that are capable of promoting proliferation in cells by modulating the hedgehog pathway and are administered to a patient suffering from severe congestive heart failure (CHF) characterized by cardiac cachexia, as well as for promoting wound healing resulting from surgery, wherein the wound heals with less scarring (column 6, formula I, column 19, lines 3-10, column 54, lines 19-25 and column 61, lines 8-27); (2) Pettet et al. teaches that angiogenesis, the formation of blood vessels, is described as a process whereby capillary sprouts are formed in response to externally supplied chemical stimuli and occurs during wound healing; and therefore, is inherently involved in Porter et al.'s method of promoting wound healing resulting from surgery; and (3) Ferrari teaches hibernating myocardium may be present over months or years, or indefinitely in subjects with fibrosis, scar formation and remodeling after myocardial infarction, wherein the therapeutic implication with regards to regional and global left ventricular function due to hibernation will improve after revascularization and it is associated with improved survival (page 52, 1st column, 2nd to 3rd paragraph). Thus, contrary to Applicants assertion that there is no common

link, the Examiner recognizes that the common link is scarring, wherein Porter clearly teaches using small organic hedgehog agonist for the promotion of wound healing, i.e., less scarring, resulting from surgery, and Ferrari provides the motivation to use these small organic hedgehog agonist following myocardial ischemia because hibernating myocardium is identified by scar formation following myocardial infarction and can be improved after revascularization, e.g., angiogenesis. Thus, one of ordinary skill in the art would have a reasonable expectation of success that by administering to a patient a small organic hedgehog agonist as taught by Porter et al. following myocardial ischemia in view of Ferrari, one would achieve a method of improving the survival of a patient following myocardial infarction. Regarding Applicants submission of relevant case law pertaining to obviousness, the Examiner acknowledges and agrees with the Federal Circuit that to render the claimed invention obvious, there must be a motivation to specifically combine the references to arrive at the claimed invention, and this motivation must be grounded in the prior art references themselves, not in Applicants' disclosure. However, as noted above, the fact patterns involved in each of these cases are different from those of the instant application. In other words, the combination of Porter et al. as evidenced by Pettet et al. in view of Ferrai et al. themselves and not Applicants' disclosure clearly provide the motivation and reasonable expectation of success to arrive at the claimed invention. Thus, Claims 1-2, 26, 37-38 and 42 **remain** rejected and new claims 43-57 **are** under 35 U.S.C. 103(a) as being unpatentable over Porter et al. (US 6,613,798, 2003) as evidenced by Pettet et al. (Proc. R. Soc. Lond. B 1996; 263: 1487-1493) in view of Ferrari et al. (Basic Res. Cardiol. 1995; 90: 52-54). In the instant case, new claims 43-47 further define the "substituents" of Formula XII, but are clearly taught by Porter et al. (see Column 7, lines 5 to lines 65). As such, claims 43-57 are included in this rejection. Moreover, claim 1 has been amended to include the limitation wherein said angiogenesis includes increased expression of vascular endothelial growth factor (VEGF). Thus, while Porter el al. do not explicitly teach the amount of a hedgehog agonist effective to promote angiogenesis, e.g., increased expression of vascular endothelial growth factor (VEGF), the claimed limitation does not appear to result in a manipulative difference between the prior arts disclosure of an effective amount to produce a therapeutic effect, e.g., promotion of would healing, being 0.0001 to about 100 mg per kilogram (column 67, lines 46-59) and the claimed limitation. Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from,

the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145. Lastly, claim 26 has been amended to recite the hedgehog agonist has a molecular weight less than 750 amu, but does not appear to overcome Porter et al. recitation of hedgehog agonist having a molecular weight of less than 750 amu (column 19, line 14).

Claims 39-41 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Porter et al. (US 6,613,798, 2003) as evidenced by Pettet et al. (Proc. R. Soc. Lond. B 1996; 263: 1487-1493) and Ferrari et al. (Basic Res. Cardiol. 1995; 90: 52-54) in further view of Igo et al. (US 5,681,278, 1997)

Porter et al. and Ferrari teach, as applied to claims 1-2, 26, 37-38 and 42-57 above, a method of improving myocardial function following myocardial ischemia, comprising administering an amount of a small organic agonist effective to promote angiogenesis. With regards to the administration, Porter et al. and Ferrari teach that the agonist may be administered systemically (Porter et al., column 67, lines 1-8).

Porter et al. and Ferrari et al. do not explicitly teach that the agonist is administered by direct injection to ischemic myocardium, intrapericardial administration or by intracoronary catheter delivery.

Igo et al. teach method for treating blood vessels in a mammal, especially the coronary blood vessels (abstract). Specifically, the patent teaches that the blood vessels can be treated by administering an agent intracoronarally to reopen the thrombosed vessel and reduce the incidence of myocardial infarction or intrapericardial injection (column 3, lines 9-16 and column 6, lines 21-22). With regards to intrapericardial injection, Igo et al. teach that many agents have been injected into the pericardial space allowing for a site specific delivery of the agent which attains higher, longer lasting drug levels in the pericardial fluid with lower plasma concentrations and less systemic toxicity (column 6, lines 23-28).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize the routes of administration of the small organic hedgehog agonist as taught by Porter et al. for the treatment of a patient following myocardial infarction. One would have been motivated to do so because it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part

II A. Moreover, as taught by Igo et al., intrapericardial administration allows for a site specific delivery of the agent which attains higher, longer lasting drug levels in the pericardial fluid with lower plasma concentrations and less systemic toxicity. Thus, one or ordinary skill in the art would have a reasonable expectation of success that by optimizing the administration routes of the small organic hedgehog agonist as taught by Porter et al., one would achieve an method of selectively targeting the blood vessels of a patient following myocardial infarction.

In response to this rejection, Applicants assert that Igo et al. fail to overcome the deficiencies of the combined teachings of Porter et al., Pettet et al. and Ferrari et al. Thus, Applicants contend that if any independent claim, for example independent claim 1, is nonobvious under 35 USC 103, then any claim depending therefrom (e.g., claims 39-41) is nonobvious.

These arguments have been carefully considered, but are not found persuasive.

Because 1-2, 26, 37-38 and 42 **remain** rejected and new claims 43-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Porter et al. (US 6,613,798, 2003) as evidenced by Pettet et al. (Proc. R. Soc. Lond. B 1996; 263: 1487-1493) in view of Ferrari et al. (Basic Res. Cardiol. 1995; 90: 52-54) for the reasons set forth above, the rejection is maintained.

New Rejections Necessitated by Amendment:

Claims 1-2, 26, 37-38 and 42-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baron et al. in view of Porter et al. (US 6,613,798, 2003) as evidenced by Pettet et al. (Proc. R. Soc. Lond. B 1996; 263: 1487-1493).

Baron et al. teach a method of treating a subject suffering from an ischemia in tissues containing mesodermally derived cells comprising administering a compound to the ischemic site so as to stimulate vascular growth, wherein the ischemia is myocardial ischemia and the compound is an agonist of a hedgehog-protein-receptor (page 5, lines 1-5 and page 53, lines 20-30). With regards to the compounds, the WO document teach that compounds of the invention include, but are not limited to, molecules which interact with membrane proteins which initiate signal transduction pathways such as smoothened, patched and gli which regulate hematopoiesis and vascular growth; and include, but are not limited to, hedgehog proteins and synthetic agonists (page 17, line 26 to page 18, line 7).

Baron et al. do not explicitly teach that the synthetic agonist is a hedgehog agonist having the formula XII with a molecular weight of less than 750 amu. Nor does Baron et al. teach that the compound is administered systemically.

Porter et al teach small organic agonist that are capable of promoting proliferation in cells by modulating the hedgehog pathway, wherein the small organic agonists encompasses the claimed small organic compounds of formula XII, as well as the claimed substituents claimed in Claims 43-57 and molecular weight (column 6, formula I, column 19, lines 3-10 and Column 7, lines 5 to lines 65). With regards to the hedgehog pathway, the patent teaches that the small organic agonist can modulate the signal transduction pathway regulated by hedgehog, pathched (ptc), gli and/or smoothened (column 18, lines 40-43). Moreover, Porter et al. teach (column 54, lines 19-25) that the small organic agonist may be administered to a patient suffering from severe congestive heart failure (CHF) characterized by cardiac cachexia, as well as for promoting wound healing resulting from surgery, wherein the wound heals with less scarring (column 61, lines 8-27). With regards to the administration, the patent teaches that the agonist may be administered systemically (column 67, lines 1-8). Thus, while Porter et al. does not teach that the administration of the agonist would promote angiogenesis, the claimed functional limitation is an inherent property of the referenced method because as evidenced by Pettet et al., "Angiogenesis, the formation of blood vessels, may be described as a process whereby capillary sprouts are formed in response to externally supplied chemical stimuli.... occurs during wound healing...." (abstract). Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). Moreover, while Porter el al. do not explicitly teach the amount of a hedgehog agonist effective to promote angiogenesis, e.g., increased expression of vascular endothelial growth factor (VEGF), the claimed limitation does not appear to result in a manipulative difference between the prior arts disclosure of an effective amount to produce a therapeutic effect, e.g., promotion of would healing, being 0.0001 to about 100 mg per kilogram (column 67, lines 46-59) and the claimed limitation. Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the references so as to use the specifically taught small organic agonists taught by Porter et al. in the method of treating a subject suffering from myocardial ischemia as taught by Baron et al.. One would have been motivated to do so because Porter et al. teach that the small organic agonist modulate the signal transduction pathway regulated by hedgehog, pathched (ptc), gli and/or smoothened (column 18, lines 40-43). Thus, one or ordinary skill in the art would have a reasonable expectation of success that by administering small organic hedgehog agonist as taught by Porter et al., one would achieve an treating a subject suffering from an myocardial ischemia.

While the instant rejection cited above has been modified as a result of the present amendement, in order to expedite prosecution the Examiner would like to address Applicants arguments pertaining to the previous rejection of Baron et al. in view of Porter et al. (US 6,613,798, 2003) as evidenced by Pettet et al. (Proc. R. Soc. Lond. B 1996; 263: 1487-1493). In response to this rejection, Applicants assert that the arguments above with respect to the rejection of the combined teachings of Porter et al., Pettet et al., and Ferrari et al. are equally applicable to this rejection. Moreover, Applicants assert that the claims have been amended to more particularly point out that the claimed method of promoting angiogenesis using an effective amount of a hedgehog agonist includes promoting increased expression of VEGF. Thus, Applicants assert given that the combined teachings of these references fail to teach or suggest each and every element of the claimed invention, the aforementioned references fail to render obvious the claimed inventions.

These arguments have been carefully considered, but are not found persuasive.

With respect to Applicants assertion pertaining to the combination of Porter et al., Pettet et al. and Ferrari et al, the Examiner's response to these assertions from above are incorporated herein. Regarding Applicants assertions with respect to the amended limitation, the Examiner recognizes, as noted above, that while Porter el al. do not explicitly teach the amount of a hedgehog agonist effective to promote angiogenesis, e.g., increased expression of vascular endothelial growth factor (VEGF), the claimed limitation does not appear to result in a manipulative difference between the prior arts disclosure of an effective amount to produce a therapeutic effect, e.g., promotion of would healing, being 0.0001 to about 100 mg per kilogram (column 67, lines 46-59) and the claimed limitation. Granting a patent on the discovery of an unknown but inherent function would remove

from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Claims 39-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baron et al. in view of Porter et al. (US 6,613,798, 2003) as evidenced by Pettet et al. (Proc. R. Soc. Lond. B 1996; 263: 1487-1493) in further view of Igo et al. (US 5,681,278, 1997).

Baron et al. in view of Porter et al. teach, as applied to claims 1-2, 26, 37-38 and 42-57 above, a method of treating a subject suffering from an ischemia in tissues containing mesodermally derived cells comprising systemically administering a compound to the ischemic site so as to stimulate vascular growth, wherein the ischemia is myocardial ischemia and the compound is an hedgehog agonist encompassed by the instantly claimed compounds of Formula XIII.

Baron et al. in view of Porter et al. do not explicitly teach that the agonist is administered by direct injection to ischemic myocardium, intrapericardial administration or by intracoronary catheter delivery.

Igo et al. teach method for treating blood vessels in a mammal, especially the coronary blood vessels (abstract). Specifically, the patent teaches that the blood vessels can be treated by administering an agent intracoronarally to reopen the thrombosed vessel and reduce the incidence of myocardial infarction or intrapericardial injection (column 3, lines 9-16 and column 6, lines 21-22). With regards to intrapericardial injection, Igo et al. teach that many agents have been injected into the pericardial space allowing for a site specific delivery of the agent which attains higher, longer lasting drug levels in the pericardial fluid with lower plasma concentrations and less systemic toxicity (column 6, lines 23-28).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize the routes of administration of the hedgehog agonist as taught by Baron et al in view of Porter et al. for the treatment of a patient following myocardial infarction. One would have been motivated to do so because it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. Moreover, as taught by Igo et al., intrapericardial administration allows for a site specific delivery of the agent which attains higher, longer lasting drug levels in the pericardial fluid

with lower plasma concentrations and less systemic toxicity. Thus, one or ordinary skill in the art would have a reasonable expectation of success that by optimizing the administration routes of the hedgehog agonist as taught by Baron et al. in view of Porter et al., one would achieve an method of selectively targeting the blood vessels of a patient following myocardial infarction.

All other rejections and/or objections are withdrawn in view of applicant's amendments and arguments there to.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Patent Examiner
Art Unit 1642

BF

12/15/2006

SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600